REMARKS

Applicants have carefully studied the Office Action mailed on July 3, 2001, which issued in connection with the above-identified application. The present response is intended to be fully responsive to all points raised by the Examiner. Favorable reconsideration and an early action on the merits is respectfully requested.

Claims 1-47 are pending and at issue in this application. The Examiner is respectfully requested to acknowledge and enter in the file history of this application a Preliminary Amendment and Response to the Restriction Requirement, which was filed by the undersigned on April 10, 2001 (copy attached as Exhibit A). In this Preliminary Amendment, claim 21 has been amended to delete an erroneous recitation of SEQ ID NO: 12, which is not a nucleic acid sequence but a peptide sequence corresponding to the substrate specificity determinant of the CASP8 small subunit (*see* the specification at page 45, lanes 14-17). In addition, claim 38 has been amended to correct a minor typographical error. Specifically, in the application as filed, claim 38 recited the "vector of claim 32". However, claim 32 is directed to a method of treating cancer and not to a vector. It is claim 36 that is directed to a vector that expresses a gene encoding functional human CASP8 in human target cells. Accordingly, claim 38 has been amended to recite the vector of claim 36. No new subject matter has been added as a result of the above-mentioned amendments.

Restriction Requirement

In the Action, the Examiner withdrew her previous Restriction Requirement and required restriction to one of the following Groups of claims under 35 U.S.C. § 121:

GroupI: Claims 1-20 and 26-29, drawn to methods of detecting inactivation of a *CASP*8 gene and corresponding kits (class 435, subclass 6).

GroupII: Claims 21-25 and 36-37, drawn to a nucleic acid sequence and corresponding expression vector (class 536, subclass 23.1 and class 435, subclass 320.1).

GroupIII: Claims 30-35, drawn to a method of treating cancer using gene therapy (class 514, subclass 44).

GroupIV: Claim 38, drawn to a pharmaceutical composition (class 514, subclass 44).

GroupV: Claims 39-47, drawn to a method of screening for a candidate compound and a corresponding kit (class 435, subclass 7.1).

In the Office Action, the Examiner contends that the inventions are distinct because allegedly (i) each method (recited in the claims of Groups I, III and V) has different starting points, steps and outcomes; (ii) the products recited in the claims of Groups II and IV have different structural features and biological functions, and (iii) the product of Group IV can be used to generate polypeptide *in vitro*, which is a materially different process of use compared to the process recited in the claims of Group III (and visa versa, the process of Group III can be practiced with another materially different product).

In order to be fully responsive to the Requirement for Restriction, applicants hereby elect, with traverse, to prosecute the claims of Group I (claims 1-20 and 26-29) directed to methods of detecting inactivation of a *CASP*8 gene and corresponding kits.

Although applicants are making the above election to be fully responsive to the Requirement for Restriction, applicants respectfully traverse the Requirement and reserve the right to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully request reconsideration of the Restriction Requirement to allow prosecution of all pending claims in the same application, or, in the alternative, modification of the Requirement to allow prosecution of more than one of the above groups, for the reasons provided as follows.

Under 35 U.S.C. § 121, "two or more independent and distinct inventions . . . in one application may . . . be restricted to one of the inventions". Inventions are "independent" if there is no distinct relationship between the two or more subjects disclosed" (MPEP 802.01). The term

"distinct" means that "two or more subjects as disclosed are related . . . but are capable of separate manufacture, use or sale as claimed, AND ARE PATENTABLE (novel and unobvious) OVER EACH OTHER" (MPEP 802.01, July 1988) (emphasis in original). However, even with patentably distinct inventions, restriction is not required unless one of the following reasons appear (MPEP 808.02):

1. Separate classification;

2. Separate status in the art; or,

3. Different field of the search.

Moreover, according to Patent Office examining procedures, "[i]f the search and examination of an entire application can be made without serious burden, the Examiner must examine it on the merits, even though it includes claims to distinct or independent inventions" (MPEP 803) (emphasis added).

Applicants respectfully submit that the Groups I-V fail to define inventions that warrant separate examination and search. Indeed, claims of Groups I , II, and V are classified in the same search class (class 435) and claims of Groups III and IV are classified not only in the same search class (class 514) but also in the same subclass (subclass 44). Accordingly, searches of claims within these two groups will be coextensive. In addition, as provided below, the claims in Groups I-V contain a number of unifying features.

Thus, methods recited in the claims of Groups I and V are based on detecting the

inactivation of the *CASP*8 gene (compare, *e.g.*, claims 2, 3, 5, and 9 of Group I with claims 43 and 44 of Group V).

Furthermore, the nucleic acid molecules recited in the claims of Group II can be used as hybridization probes or PCR primers to detect the inactivation of the *CASP*8 gene according to the methods of Groups I and V (*see, e.g.*, claims 24 and 25 directed to *CASP*8 promoter-specific PCR primers and labeled *CASP*8-specific hybridization probes, respectively). Indeed, as recited in claims 28 and 29 (Group I), a kit for detecting inactivation of the *CASP*8 gene comprises PCR primers and hybridization probes recited in claims 24 and 25 (Group II).

In addition, the CASP8 expression vectors recited in claims 36 and 37 (Group II) can be used in the gene therapy method recited in the claims of Group III as well as in the pharmaceutical composition recited in claim 38 (Group IV). In fact, claim 38 as amended refers back to claim 36 and therefore shares patentability issues with this claim.

In light of the foregoing arguments, it can be concluded that the claims of provisionally elected Group I contain multiple unifying features with the claims of Groups II-V, and, in particular, with the nucleic acid claims of Group II and diagnostic method claims of Group V. Hence, it is believed that a single search of the features of the methods recited in the claims of Group I would necessarily and unescapably require a search of the subject matter of the claims of Groups

II and V, and will overlap with the search of the subject matter of Groups III and IV.

If Group I is elected, the Examiner further requests election of a means of detection, wherein a protein is detected, or wherein a polynucleotide is detected. To be fully responsive to the Office Action, applicants elect with traverse polynucleotide detection. Although applicants are making the above election to be fully responsive to the Restriction/Election Requirement, applicants respectfully traverse the Requirement and reserve the right to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully note that detection of both nucleotides and peptides is a standard practice in the art, which, only if taken in combination, can reveal all aspects of the control of gene expression. For example, only by combining the immunodetection of CASP8 protein, Nothern blot analysis of *CASP8* mRNA, and methylation-sensitive PCR analysis of *CASP8* gene promoter, a person of ordinary skill in the art can determine with confidence whether the absence of a proper CASP8 protein function is due to transcriptional silencing, genomic mutation, improper posttranslational modification, or some other reason.

Applicants are aware that, if, based on the arguments presented above, the Examiner decides to modify the Restriction Requirement to consider the nucleic acid claims of Group II[1]

[1] In view of the previous Restriction Requirement mailed on March 14, 2001 (paper No. 9), applicants believe that the recitation "Group III" at page 4 of the present Office Action is a typographical error.

together with the method claims of Group I, the Examiner may request election of a single species of nucleic acid sequences from SEQ ID NOS: 1-10 and 12-28[2] accompanied by a statement of what type of sequence (*i.e.*, intron, exon, promoter, etc.) the species is generic to[3]. In order to be fully responsive to such potential Requirement, applicants hereby elect, with traverse, the *CASP*8 promoter sequence SEQ ID NO: 2.

Although applicants are making the above election to be fully responsive to a potential Restriction/Election Requirement, applicants respectfully traverse the Requirement and reserve the right to petition therefrom under 37 C.F.R. § 1.144. In particular, applicants respectfully submit that the Restriction/Election Requirement is not proper because SEQ ID NOS: 1-10 and 13[2]-28 represent large (SEQ ID NOS: 1-10) or small (SEQ ID NOS: 13-28) fragments of the same continuous *CASP*8 genomic sequence, and have been provided separately exclusively for convenience (*see, e.g.*, page 10, lanes 3-11 and Table 1 at page 45, lanes 18-30). Indeed, as disclosed at page 43, lanes 12-22, these sequences represent portions of a single *HindIII* fragment containing the entire gene, which was isolated from BAC genomic library and subcloned into pKS

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[2] In the Preliminary Amendment and Response to the previous Restriction Requirement (filed on April 10, 2001, copy attached as Exhibit A), claim 21 has been amended to delete the recitation of SEQ ID NO: 12, which should not be grouped with nucleic acid sequences, because it is a peptide sequence corresponding to the substrate specificity determinant of the CASP8 small subunit (*see* the specification at page 45, lanes 14-17).

[3] This Restriction/Election Requirement is stated at page 4 of the present Office Action.

plasmid for sequencing. Accordingly, the search and examination of each of the sequence species from SEQ ID NOS: 1-10 and 13-28 would be necessarily co-extensive, and can be made without undue burden on the Examiner.

Furthermore, as specified in MPEP 803.04 (emphasis added): "to further aid the biotechnology industry in protecting its intellectual property without creating an undue burden on the Office, the Commissioner has decided sua sponte to partially waive the requirements of 37 CFR 1.141 et seq. and permit a reasonable number of such nucleotide sequences to be claimed in a single application. See Examination of Patent Applications Containing Nucleotide Sequences, 1192 O.G. 68 (November 19, 1996). It has been determined that normally ten sequences constitute a reasonable number for examination purposes. Accordingly, in most cases, up to ten independent and distinct nucleotide sequences will be examined in a single application without restriction."

In light of the foregoing practice, a potential Examiner's requirement to elect a single sequence is traversed. It is believed that the applicants are entitled to election of all sequences comprising SEQ ID NOS: 1-10 and 13-28.

In closing, applicants respectfully submit that the groups of claims designated by the Examiner fail to define methods and compositions that warrant separate examination and search. The present claims represent a web of knowledge and continuity of effort that merits examination in a single application. Thus, the search and examination of each group is necessarily co-extensive, and in any event would involve such interrelated art that the search and examination of the entire application can be made without undue burden on the Examiner. Accordingly, applicants

respectfully request that the Examiner withdraw the Requirement for Restriction and examines all of the pending claims in a single application or at least modifies the Requirement to allow prosecution of more than one of the above groups.

CONCLUSION

Applicants request entry of the foregoing remarks in the file history of this application. In view of the above arguments, withdrawal or modification of the Requirement for Restriction is respectfully requested, and an early action on the merits is courteously solicited.

Respectfully submitted,

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